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Dated 6 June 1995

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Request for grant of a Patent

Form 1/77

Patents Act 1977

1 Title of invention

1 Please give the title of the invention

RECOMBINANT ANTIBODIES FOR DELIVERY OF IMMUNODOMINANT PEPTIDES

2 Applicant's details

2 Do not give trading styles, for example, 'Trading as XYZ company', nationality or former names, for example, 'formerly (known as) ABC Ltd' as these are not required.

First or only applicant

2a If you are applying as a corporate body please give:

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UK postcode *(if applicable)* AB1 2YG

Country U.K

ADP number *(if known)* 6602203001

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please give details below

Agent's name KEITH W NASH + CO

Agent's address PEARL ASSURANCE HOUSE
90-92 REGENT STREET
CAMBRIDGE CB2 1DP

Postcode

Agent's ADP number 1206001

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4 Agent's or applicant's reference number *(if applicable)*

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5 Are you claiming that this application be treated as having been filed on the date of filing of an earlier application?

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Yes [✓] No [ ] ➡ ***go to 6***

please give details below

❑ number of earlier application or patent number 9409643.5

❑ filing date 13 05 94
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❽ *Please supply duplicates of claim(s), abstract, description and drawing(s).*

❽ Checklist

8a Please fill in the number of sheets for each of the following types of document contained in this application.

Continuation sheets for this Patents Form 1/77			
Claim(s)		Description	8
Abstract		Drawing(s)	9

8b Which of the following documents also accompanies the application?

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Priority documents *(please state how many)*	
Translation(s) of Priority documents *(please state how many)*	
Patents Form 7/77 – Statement of Inventorship and Right to Grant *(please state how many)*	
Patents Form 9/77 – Preliminary Examination/Search	
Patents Form 10/77 – Request for Substantive Examination	

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Recombinant Antibodies for Delivery of Immunodominant Peptides

The invention relates to a new type of recombinant antibody or protein designed for the efficient delivery of one or more immunodominant (antigenic) peptide molecules to a target cell for subsequent antigen presentation by the target cell and either induction or inhibition of an immune response. In particular, the invention relates to recombinant antibody or protein molecules containing immunodominant peptide sequences whereby these antibody or protein molecules enter cells via internalising antigens or receptors and are subsequently processed to release peptides for antigen presentation. The invention also relates to recombinant antibodies or proteins modified in order to facilitate the attachment of immunodominant peptides for delivery into the target cell. The invention also relates to methods for treatment and prevention of disease using these new types of recombinant antibodies or proteins and methods for generating these molecules.

The finding that T-cells recognise antigen as peptides bound to major histocompatability complex (MHC) molecules has given rise to attempts to use defined synthetic peptides corresponding to immunodominant T-cell epitopes to either activate or tolerise T-cells to specific antigens. Invariably, the approach used has been to immunise with the immunogenic peptide in order to induce a T-cell response relying on the efficient processing and antigen presentation by professional immune system cells to induce a T-cell response comprising either a predominant response by CD8+ cytotoxic T lymphocytes (CTL's) for peptide presented in conjunction with MHC class I molecules or a predominant CD4+ helper T-cell response for peptide presented in conjunction with MHC class II molecules. For the treatment of cancer, there is now a major interest in the induction (or adoptive transfer) of CTL's specific for tumour-associated antigens such as the MAGE-1 antigen produced by a high proportion of human melanoma tumours (van der Bruggen et al., Science 254 (1991) p1643). There is also an interest in the identification of peptides associated with diseases such as autoimmunity in order to induce tolerance by administration of the autoimmune peptide and subsequent presentation and overstimulation leading to abrogation of peptide-specific CTL's (e.g. Aichele et al., PNAS 91 (1994) p444). There is additionally an interest in the identification of peptides associated with diseases such as allergy in order to redirect a TH2 response induced by the allergan to a TH1 response by immunising with a peptide homologue of the TH1-inducing epitope. Another approach is to immunise with altered peptides which, upon presentation, can bind to but not activate a specific T-cell thus antagonising deleterious responses of such T-cells, for example to superantigens critical to the infectious action of a number of bacteria and viruses via activation of specific T helper cells (e.g. Evavold et al., PNAS 91 (1994) p2300).

There are 3 main limitations to the direct use of peptides for activation or tolerance of specific T-cells to antigens involved in disease processes. Firstly, peptide-induced activation of cytotoxic T cells for the subsequent destruction of aberrant disease-associated target cells is restricted to target cells which present the specific peptide, usually professional (constitutive) or facultative antigen presenting cells and also cells such as cancer cells expressing the MAGE-1 antigen. Thus, it is currently not possible to direct the activation of T cells by antigen presentation by specifically

chosen cell types. Secondly, peptide-induced activation or tolerance relies on the efficient uptake and presentation of peptide by professional or facultative antigen presenting cells: the efficiency of presentation is highly dependant on factors such as peptide concentration and peptide formulation with adjuvants which are variable for different peptides and do not always result in a specific T-cell response. Thirdly, peptide presentation is MHC-restricted and dependant on specific HLA type and thus the activation or tolerance of T cells to a certain immunodominant peptide is dependant on the HLA type of the individual.

Instead of relying on individual peptides finding and being presented by professional or facultative antigen-presenting cells, the present invention uses antibody or protein molecules specific for internalising antigens or receptors on any cell type to deliver one or more peptides internally to these cells. Upon digestion and processing of the recombinant antibody/protein-peptide molecules, the peptides can then be presented in the presence of appropriate MHC molecules. Specifically, the present invention relates to a new class of antibody or protein molecule produced, by recombinant DNA methods, to preferably include within the protein the sequence of one or more immunodominant peptides, or to alternatively include modifications specifically for the efficient attachment of one or more peptide molecules. Thus the invention provides, for the first time, a means of targeting antigen presentation to a particular chosen cell with the main requirement of an internalising antigen or receptor bound by an antibody or protein containing the peptide antigen to be presented (optimally in multiple copies).

Advantages of the present invention for the activation or tolerance of T-cells are several-fold. Firstly, by using an antibody or protein to deliver immunodominant peptides, these peptides can be delivered, via an internalising antigen, to cells which do not normally present such peptides. In the case of cancer cells for example, a cancer cell can then present one or more peptides designed to activate CTL's to subsequently destroy the cancer cell. In the case of normal cells subject to autoimmune destruction by CTL's, these peptides can be delivered via an internalising antigen or receptor either as high doses of normal immunodominant peptides to induce tolerance by abrogation of the usually destructive CTL's or as altered peptides which antagonise the disease-associated T-cell activation. Secondly, several different peptide sequences or multiple copies of the same peptide sequence can be associated with a single antibody or protein molecule, the former providing the prospect for a choice of peptides for presentation by the appropriate MHC haplotype in the individual immunised and the latter providing the prospect for efficiently delivering a high dose of peptide via multiple copies on the antibody molecule. Thirdly, by using an antibody or protein to deliver immunodominant peptides, these peptides can be efficiently delivered, via an internalising antigen, to specific professional antigen presenting cells as an alternative to the less specific endocytosis by these cells; thus, the presentation of antigens can be more focused in order to better control the type of immune response to the immunodominant peptide.

It will be understood that the present invention can apply to both class-I and class-II MHC-restricted immunodominant peptides and can potentially be applied to the targeted induction of an immune response to many different antigens in many different disease states such as cancer (induction of CTL's by cancer cells),

autoimmunity (antagonism of T-cell activation or induction of tolerance), infection (induction of CTL's by infected cells, antagonism of T helper cell activation by superantigens), allergy (diversion of a TH2 to a TH1 response by the immunodominant peptide) and inflammation (antagonism of T-cell activation). It will also be understood that antibodies or proteins produced by the present invention could include the so-called "universal" immunodominant peptides (e.g. tetanus toxin and influenza nucleoprotein peptides) against which a high proportion of individuals might already be sensitised to by vaccination or infection. It will also be understood that, for efficient presentation of MHC class I-associated peptides by antibodies or proteins produced by the present invention, the inclusion in the molecule of sequences facilitiating entry of these peptides into the cytoplasm from compartments such as the endosomes or trans golgi network may be required and that certain such sequences (or domains) already known in the literature (such as the translocation domains of toxins such as Pseudomonas exotoxin (Donnelly et al., PNAS, 90 (1993) p3530), the HIV-1 Tat protein (Fawell et al., PNAS, 91 (1994) p664) or the endosome-disrupting functions of viruses such as adenovirus (Curiel et al., PNAS, 88 (1991) p8850). It will also be understood that antibodies or proteins produced by the present invention could include a mixture of different peptides which associate with different MHC class I or class II molecules thus providing for a broader prospect of inducing an immune response in different population groups carrying different HLA types. It will also be understood that the antibodies or proteins of the present invention could be used in several different ways in disease treatment and prevention including to deliver peptides *ex vivo* for the induction of CTL's prior to adoptive immunotherapy and to enhance the T-cell activating, blocking or abrogating ability of cells already presenting the specific peptide(s) or analogues thereof. It will be understood that antibodies or proteins of the present invention could be targeted to professional antigen presenting cells such as, for example, macrophages (e.g. via the FcRI receptor) and B cells (e.g. via surface immunoglobulin molecules). Finally, it will be understood that the antibodies or proteins of the present invention might be used for disease treatment or prevention either alone or in combination with other molecules which potentiate the interaction with T-cells such as molecules which up-regulate class I and class II MHC expression in certain cell types such as interferon-gamma or that the antibodies or proteins of the present invention might themselves be used as vaccines through the inclusion of adjacent immunodominant B and T-cell epitopes optimally as multiple copies and targeted to professional antigen presenting cells.

It will be understood by those skilled-in-the-art that immunodominant peptides might be included at many different locations in the antibody molecule via recombinant DNA or might alternatively be conjugated to the antibody molecule via natural amino acid residues or via amino acid residues incorporated by recombinant DNA for subsequent conjugation. It will be understood that incorporation or conjugation of these peptides should be such that, as required, antibody function such as binding affinity and rate of clearance is not impaired. Alternatively, it will be understood that peptides could be incorporated as part of an incomplete recombinant antibody fragment such as a Fab, a Fv or a SCA (single chain-antibody) fragment. Depending on the application, it might be preferable to include the immunodominant peptides in a protein domain or structure designed to either mask the peptides from specific recognition by circulating or cell-bound molecules or to expose the peptides such that

some immune recognition is possible instead of direct uptake by an internalising antigen. For peptides which particularly stimulate a good B-cell response following internalisation and presentation (particularly MHC class-II restricted), it might be preferable to mask the peptides from specific recognition by circulating antibodies in order to avoid premature clearance by the immune system. Finally, it will be understood that internalisation of immunodominant peptides might be achieved via a recombinant bispecific (or multispecific) antibody comprising at least one specificity for the internalising antigen and at least one other specificity for the immunodominant peptide or peptide structure which is bound by the bispecific antibody prior to administration; in addition, it will be understood that a bivalent (or multivalent) antibody might be used consisting of one part binding to the internalising antigen and another part with no specific binding specificity but including the immunodominant peptide either within or attached to the antibody structure (including immunodominant peptides insertion at the usual sites for CDRs (complementarity-determining regions).

Figures 1 to 8 illustrate a number of possible designs for antibodies including immunodominant peptides either in discrete multi-peptide domains (figure 1 to 7) or as individual peptide sequences included to replace CDRs (figure 8). These figures should not be considered an exclusive set of designs for antibodies containing immunodominant peptides and should not be considered as limiting the scope of the invention. For these figures, antibodies are drawn comprising CDRs (complementarity-determining regions), VH and VL domains i.e. variable region heavy and light chain domains (including the CDRs), CL domains i.e. light chain constant domains, and CH1-3 i.e. heavy region constant domains.

Figure 1: this illustrates an antibody whereby the immunodominant peptide domain including multiple copies of the same immunodominant peptide or, alternatively, individual copies of multiple peptides (for example, to compensate for MHC-restriction by providing a range of options covering different MHC haplotypes). has been fused adjacent to the hinge region in the heavy chains upstream from the CH2 domains.

Figure 2: this illustrates an antibody whereby the immunodominant peptide domain has been fused adjacent to the hinge region in the heavy chains thus replacing the CH2 and CH3 domains to create a Fab-peptide hybrid antibody.

Figure 3: this illustrates an antibody whereby the immunodominant peptide domain has been fused adjacent to the hinge region in the heavy chains replacing the CH2 domains.

Figure 4: this illustrates a SCA (single-chain antibody) whereby the immunodominant peptide domain has been fused adjacent to a recombinant Fv via a linker arm.

Figure 5: this illustrates an antibody whereby the CH3 domain has been replaced by the immunodominant peptide domain.

Figure 6: this illustrates an antibody whereby the immunodominant peptide domain has been fused adjacent to the VL region in the light chains thus replacing the CL domains

Figure 7: this illustrates a bispecific antibody created by either the coexpression or thiol reduction/oxidation of a mixture of antibody heavy chains whereby in one the immunodominant peptide domain has been fused adjacent to the hinge region thus replacing the CH2 and CH3 domains.

Figure 8: this illustrates an antibody whereby 6 copies (or 6 variants) of the immunodominant peptide have been inserted in the VH VL regions to replace the CDRs.

Figure 9: this illustrates the typical organisation of an immunodominant peptide domain for HLA class I-associating peptides whereby several peptide copies arranged in a contiguous fashion are fused to a translocating domain (D) and a C-terminal KDEL-like sequence.

The peptide domains referred to in figures 1 to 7 and depicted in figure 9 above could comprise either multiple repeats of the same immunodominant peptide or a range of different immunodominant peptide sequences within the same domain. In each case, the peptide sequences may be repeated in head-to-tail or head-to-head organisation with suitable amino acid spacing between the sequence repeats provided by non-immunodominant sequences. In each case, the immunodominant peptide content of heavy and light chains might be the same or different and peptide domains may be added to one of only the heavy or light chains or in one of these chains only or as part of a bispecific (or multispecific) antibody whereby the peptide domains might only be derived from one or more of the recombinant chains used to create the bispecific. It will be understood that the arrangement of immunodominant peptide sequences in the peptide domain might require optimisation for different peptides included in the domain and might need to be optimised in order to ensure efficient production of the recombinant antibody without disruption of the antibody-like structure. It will also be understood that optimisation of antibodies for effective processing of the immunodominant peptide domains might also be required. In each case, optimisation might require different arrangements of peptides in conjunction with each other, different flanking amino acid sequences between the immunodominant peptides (including introduction of sequences to promote cleavage upon internal processing outside the immunodominant peptide regions) and different combinations with other peptide or protein structures as required for reasons such as to keep the total molecule from misfolding or to keep the immunodominant peptides either internalised or externalised in a globular protein structure. It will also be understood that, for HLA class I-associating peptides, the addition of a translocating domain (or domains) adjacent to the tandemly-arranged peptides might be required for efficient transport to and processing in the cytoplasm.

The following examples serve to illustrate the possible applications of antibodies of the present invention and should not be considered as limiting the scope of the invention.

Example 1:
The generation of recombinant monoclonal antibodies suitable for use in treatment and prevention of human disease has been comprehensively described in the literature (for example Boulianne et al., Nature 312 (1984) p643; Morrison et al., PNAS 81 (1984) p6851; Reichmann et al., Nature 332 (1988) p323; Queen et al., PNAS (1989) p10029) and methods have been developed for production of whole antibodies from mammalian and other eucaryotic cells and also for production of antibody fragments (e.g. Fv's, Fab's, SCA's) from E coli. For generation of antibodies from mammalian cells, all of the antibody designs depicted in figures 1 to 3 and 5 to 8 can be produced. Methods for generation of bispecific antibodies as depicted in figure 7 are also known in the art for mammalian cells and bispecific antibody fragments can also be generated from bacteria. In one example, the antibody of figure 1 could be generated to include tandem-repeated multiple copies of the CTL-inducing nonapeptides derived from the genes, MAGE-1, 2 and 3 (van den Eynde et al., Int J Cancer 44 (1989) p643) with suitable spacing provided by short runs of non-immunodominant amino acids between the immunodominant peptides and with adjacently provided translocating domains such as from the HIV-1 Tat protein. This could then be administered to a patient types as HLA-A1 harbouring a cancer with an internalising antigen (such as Lewis-Y) such that the antibody will internalise into the tumour and will potentially present the MAGE nonapeptides to the immune system. This may then activate MAGE-specific CTL's which will then lyse the tumour; alteratively, the patient could be preimmunised with MAGE peptides or an antibody such as in example 3 in order to expand and preactivate MAGE-specific CTL's.

Example 2:
As an alternative to example 1, antibodies could be generated in the same manner but containing class-II MHC restricted peptides such as the tetanus toxin peptide P2 (Panina-Bordignon et al., Eur J Immunol 19 (1989) p2237) and excluding the cytoplasm translocating domain. Such antibodies would be administered to a cancer patient with an appropriate HLA-DR type for presentation of P2. If the antibody is again specific for an internalising antigen on the cancer cells, then the antibody will internalise into the tumour and will potentially present the P2 peptides to the immune system. This may then activate P2-specific T helper cells to release lymphokines and to activate B cells and also may activate CTL's which will then lyse the tumour; in addition, a greater antitumour response may be generated if the patient is preimmunised with P2 peptide or an antibody such as in example 3 in order to expand and preactivate P2-specific CTL's.

Example 3:
As alternatives to examples 1 and 2, antibodies could be generated in the same manner but with specificity for an internalising antigen on professional antigen-presenting cells, such as specificity for MHC class II antigen or specificity for surface-Ig on B cells, and including peptides presented by, for example cancer cells (e.g. for MAGE 1-3, a high proportion of human malignant melanoma cancers). If administered to a cancer patient with an appropriate MHC type for presentation of the peptides carried within the antibody, these should be processed and presented to the immune system by the antigen-presenting cells which would then stimulate an immune response against the cancer antigen represented by the peptides presented. In addition, antibodies from examples 1 and 2 might be used in combination with the

type of antibody of this example in order to efficiently present the antigen on the target cancer cells for effective activation of T cells.

Example 4:
As alternatives to examples 1 to 3, antibodies could be generated in the same manner for use in autoimmune diseases where the autoimmune immunodominant peptides are known. For example, T cells involved in the deterioration of normal tissue in the disease could be deleted or inhibited by creating an antibody specific for an internalising antigen on a professional antibody producing cell as in example 3 or by targeting the cells of the tissues subject to deterioration (e.g. thyroid cells via the TSH receptor for Graves Thyroiditis). In each case, the antibody would include multiple copies of the autoimmune immunodominant peptide to induce tolerance or would include altered peptides which, upon presentation, can bind to but not activate the deleterious T-cell thus inhibiting autoimmunity.

Example 5:
As an alternative to example 3, antibodies could be generated with specificity for an internalising antigen on professional antigen-presenting cells, such as specificity for MHC class II antigen or specificity for surface-Ig on B cells, and including immunodominant peptides derived from infectious disease agents (e.g. the HIV V3-loop epitope conserved in a high proportion of HIV isolates). If administered to an infected patient with an appropriate MHC type for presentation of the peptides carried within the antibody, these should be processed and presented to the immune system by the antigen-presenting cells which would then stimulate an immune response against the infectious agent. Indeed, antibodies used in this manner might constitute effective vaccine agents as an alternative to vaccines comprising peptides or live/attenuated infectious agents which might not be efficiently processed by antigen-presenting cells.

Example 6:
As an alternative to example 3, antibodies could be generated with specificity for an internalising antigen on professional antigen-presenting cells and including immunodominant peptides derived from allergens which normally induce a TH2 allergenic response. If administered preferably to the mucosal surfaces of a sensitised patient with an appropriate MHC type for presentation of the peptides carried within the antibody, these should be processed and presented to the immune system by the antigen-presenting cells which would then stimulate the induction of TH1 cells in preference to TH2 cells thus alleviating the allergenic response to the allergen. Indeed, antibodies used in this manner might constitute effective vaccine agents as an alternative to vaccinating with allergen preparations which might not be efficiently processed by antigen-presenting cells.

Example 7:
As an alternative to example 3, antibodies could be generated with specificity for an internalising antigen on professional antigen-presenting cells and including immunodominant peptides derived from autoimmune antigens which normally induce a T helper response. If administered to an afflicted patient with an appropriate MHC type for presentation of the peptides carried within the antibody, these should be processed and presented to the immune system by the antigen-

presenting cells which would then induce tolerance in the T helper clones responsible for the autoimmune response. Indeed, antibodies used in this manner might constitute effective alternatives to peptide vaccines.

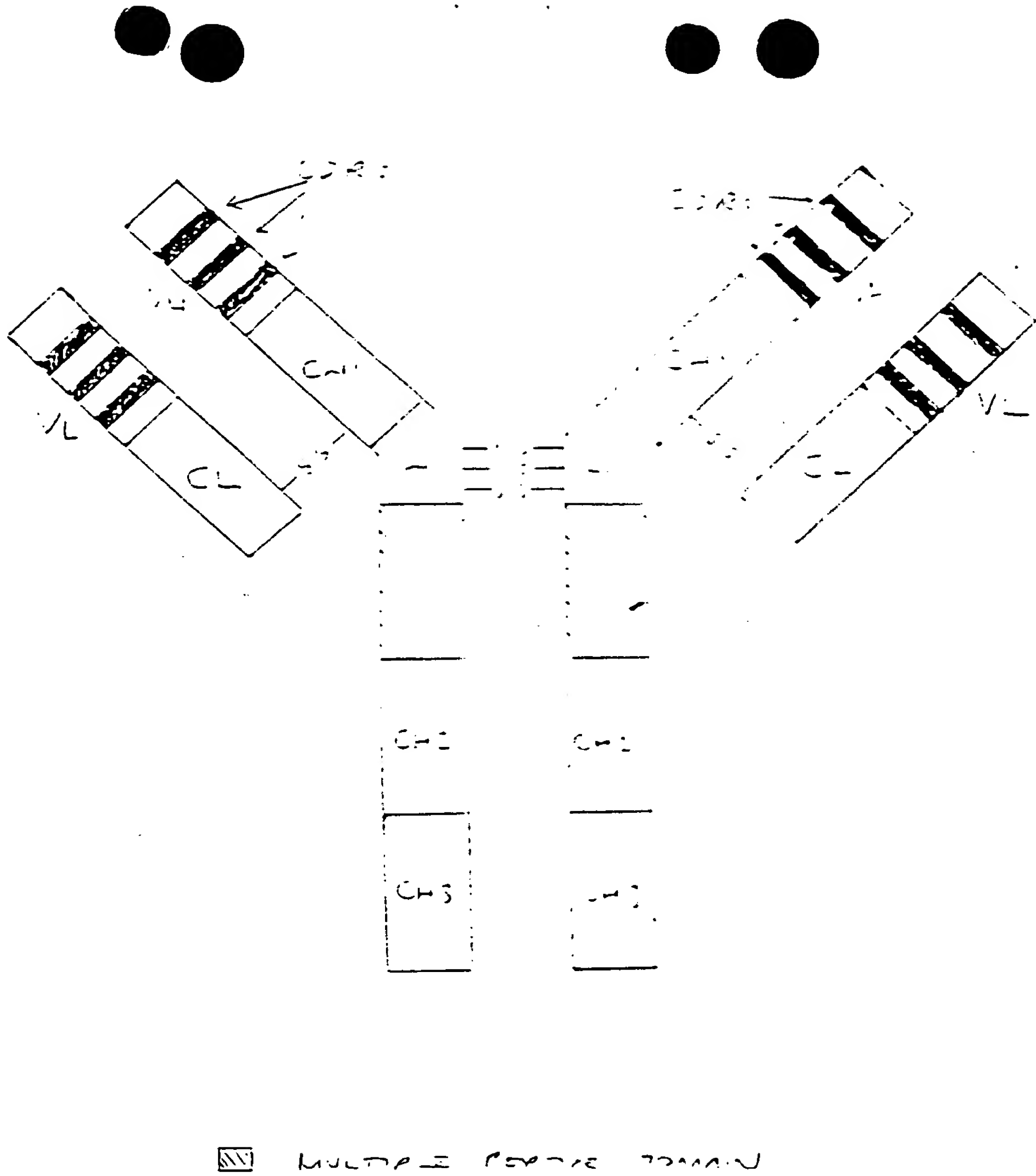


Fig 1

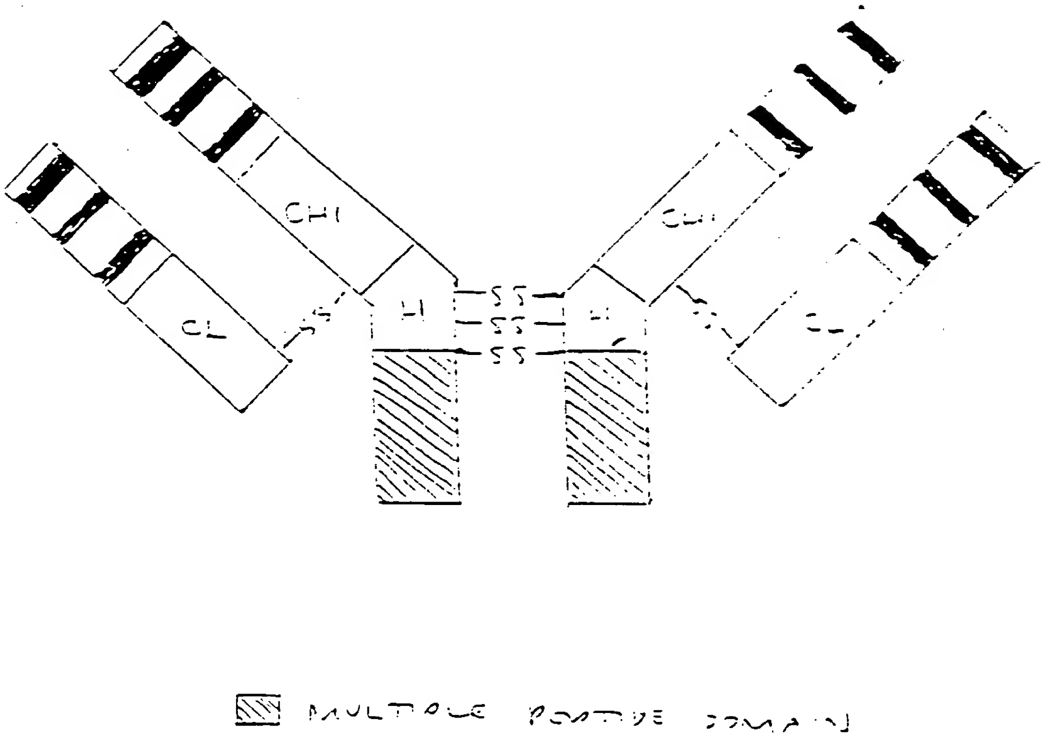
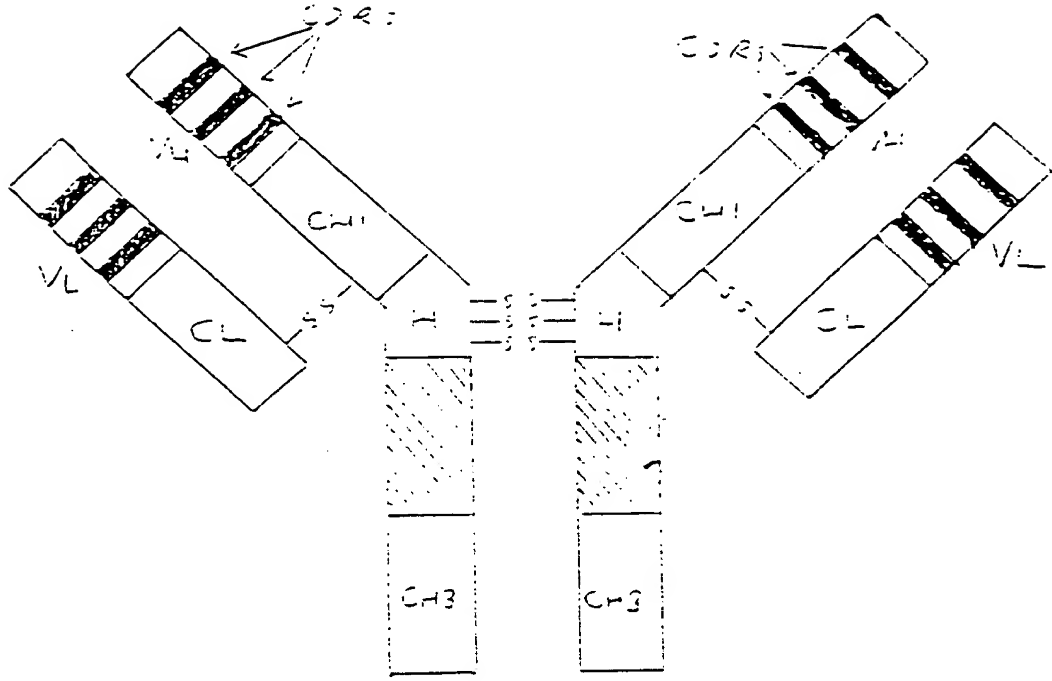


Fig 2



MULTIPLE PEPTIDE DOMAIN

Fig 3

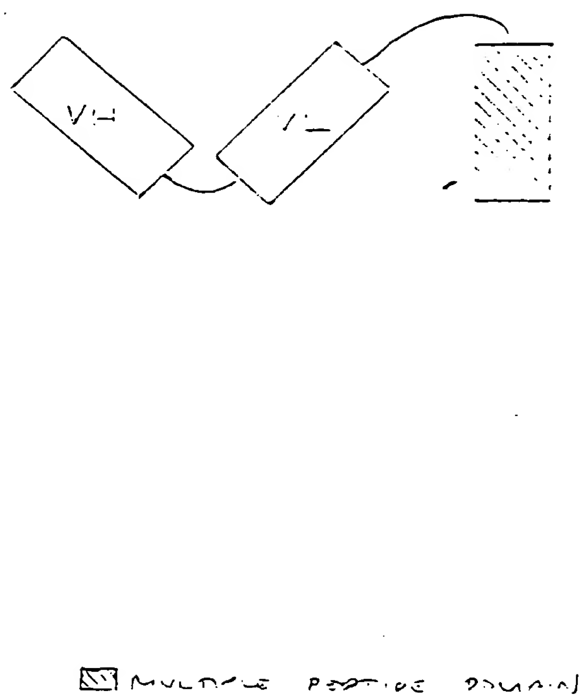


Fig 4

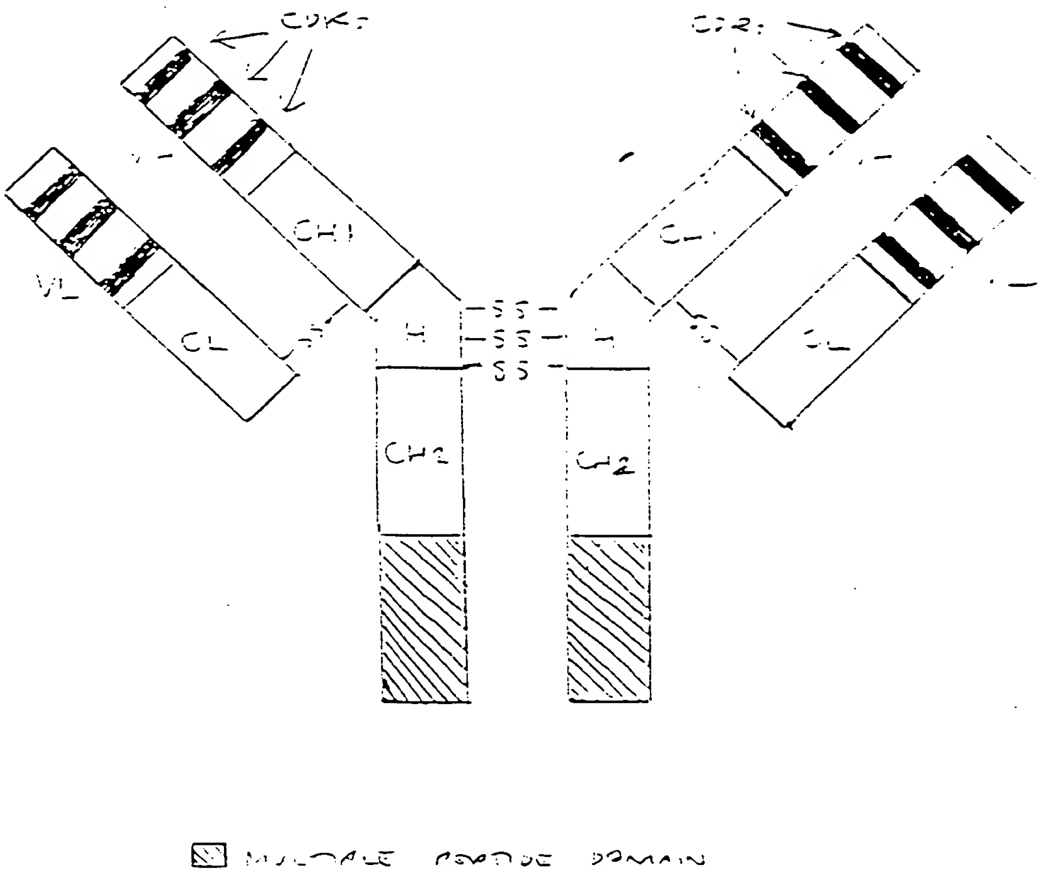


Fig 5

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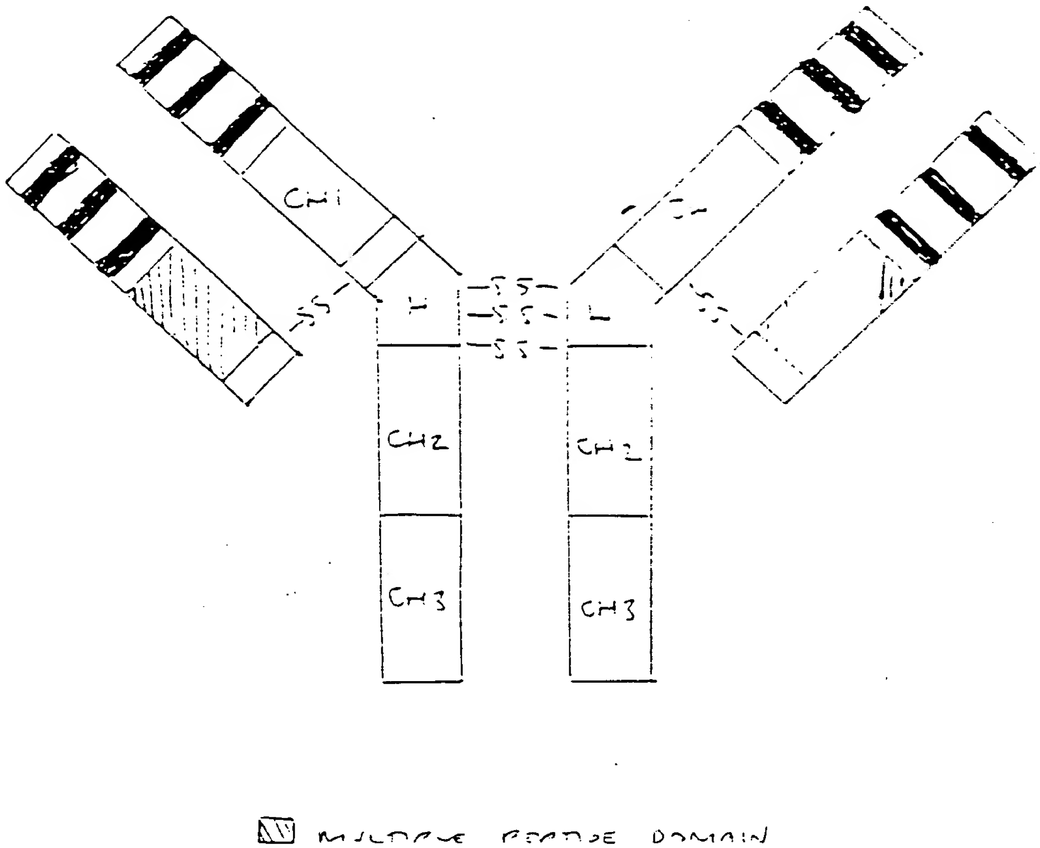

Fig 6

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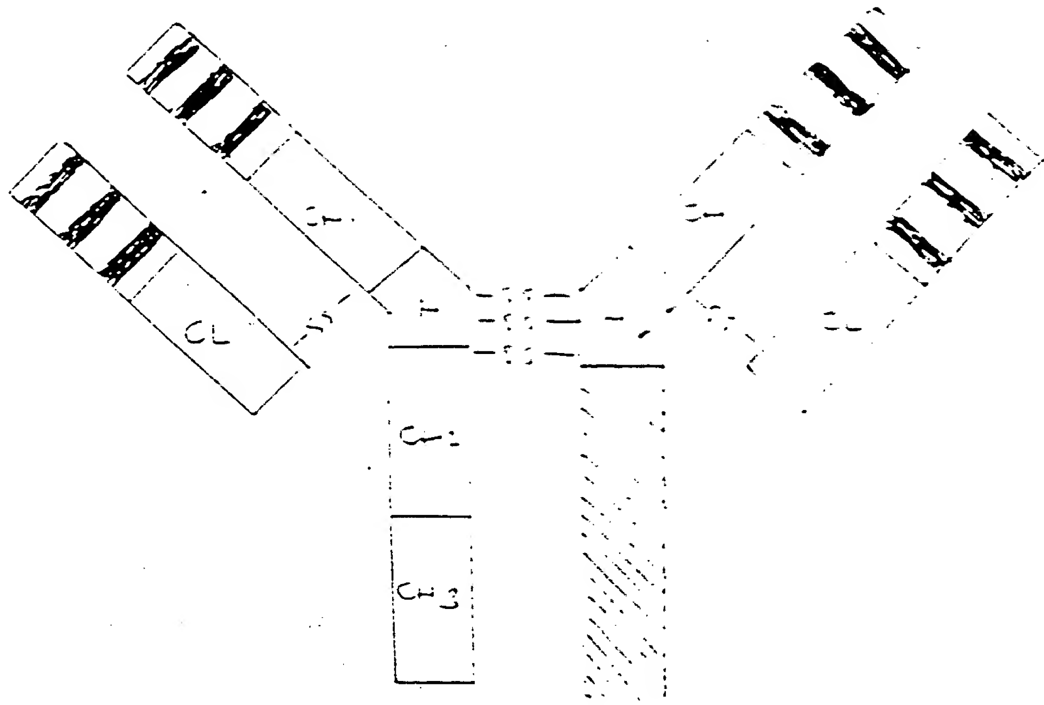

MULTIPLE EPITOPE DOMAIN

Fig 7

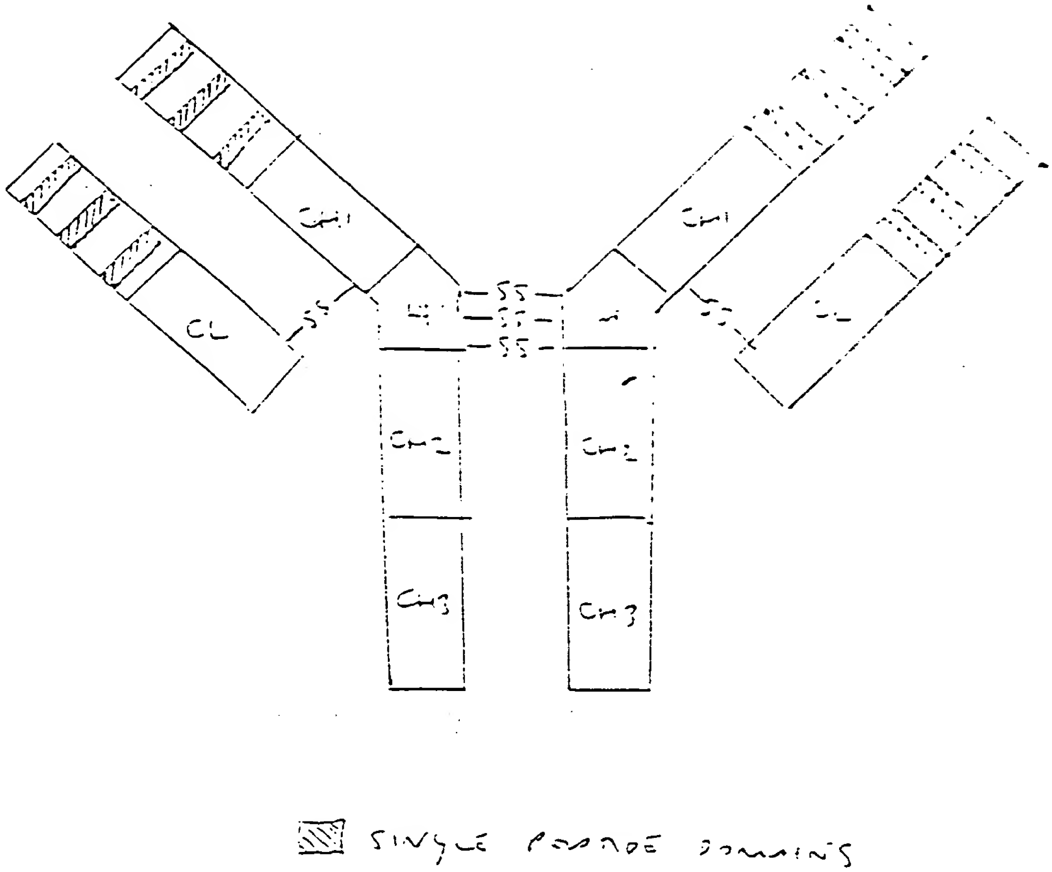

Fig 8

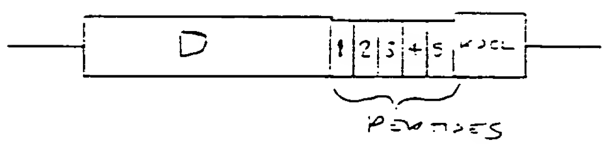

Fig 9

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